PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The rationale and design of a cross-sectional study to investigate and describe the Chronotype of Patients with Type 2 Diabetes and the Effect on Glycaemic Control: The CODEC study
AUTHORS	Brady, Emer M.; Hall, Andrew; Baldry, Emma; Chatterjee, Sudesna; Daniels, Lois; Edwardson, Charlotte; Khunti, Kamlesh; Patel, Mubarak; Henson, Joseph; Rowlands, Alex; Smith, Alice; Yates, Thomas; Davies, Melanie

VERSION 1 – REVIEW

REVIEWER	Freda Patterson University of Delaware, USA
REVIEW RETURNED	24-Mar-2019

GENERAL COMMENTS	Manuscript Review Bmjopen-2018-027773: The rationale and design of a cross-sectional study to investigate and describe the Chronotype of Patients with Type 2 Diabetes and the Effect on Glycaemic Control: The CODEC study This manuscript describes a protocol to characterize the cardiometabolic profile of adults with Type 2 Diabetes who are early versus late chronotype. Specifically, 2247 primary care patients will be enrolled and objective assessments of glycaemic control, some cardiometabolic health metrics and self-reported assessments of well-being and lifestyle factors will be taken and compared across different chronotype profiles. Strengths of this protocol include the focus on sleep chronotype and its relationship with type 2 diabetes and other cardiometabolic metrics. This is a critical area of study, and sleep chronotype, is a poorly understood sleep metric. It is expected that that the results of this cross-sectional study will provide chronotype-based phenotypes for type-2 diabetes that could ultimately advance our understanding of the role of sleep in chronic disease. Limitations of this protocol are itemized below. 1. What is the rationale for the inclusion of physical fitness assessments? How do these assessments relate to the study aims and hypotheses? 2. What is the rationale for the genetic analysis? How do these assessments relate to the study aims and hypotheses?

	3. What is the rationale for 8-days of accelerometer wearing as opposed to the recommended 10 or 14 days? Two weekend assessments are necessary to fully examine social jetlag metrics. 4. Why is chronotype not being calculated from the accelerometer data? An objective assessment of chronotype would be superior. 5. The authors are strongly encouraged to consider household and environmental determinants of chronotype (and sleep in general) including (but not limited to) family composition, bedroom climate, neighborhood factors, and geographic positioning. Omission of these variables limits the scientific rigor of this study. 6. It is not clear why these research questions were not just presented to the UK Biobank? 7. There are typos and formatting errors in the references.

REVIEWER	Yeong-Mi Seo South Korea
REVIEW RETURNED	22-Aug-2019

GENERAL COMMENTS	The criteria for person 's chronotype must be clear. People's lifestyles change. Therefore, there are many limitations to the interpretation of the results.

VERSION 1 – AUTHOR RESPONSE

Response
Reviewer 1
1. What is the rationale for the inclusion of physical fitness assessments? How do these assessments relate to the study aims and hypotheses?
We thank you for this query and agree it is not well described in the manuscript. To expand we have added this paragraph into the introduction;

Further, individual components of phenotypic frailty, such as handgrip strength and walking pace, and composite scores such as SPPB, are established risk factors for mortality, morbidity and disability [1, 2]. More generally, frailty, regardless of how it is defined, is associated with incident falls, difficulty with activities of daily living, disability, hospitalisation and death [3]. Whilst T2DM itself is associated with an elevated risk of mortality and health care utilisation, frailty magnifies these risks [4]. It is important to determine if there is an interaction between parameters of sleep, T2DM and individual components of frailty.
We have made the following additional amendments to the manuscript.
Last paragraph of introduction (page 4) changed from:
This will build on the existing evidence base and permits exploration of the interrelationship between sleep behaviours, glycaemic control, cardiometabolic health and other lifestyle factors including wake-time activity and temporal eating habits in a multi-ethnic cohort with established T2DM

To

This will build on the existing evidence base and permits exploration of the interrelationship between sleep behaviours, glycaemic control, cardiometabolic health, physical fitness and other lifestyle factors including, wake-time activity and temporal eating habits in a multi-ethnic cohort with established T2DM

Page 5 line 6 we have added;
…health and other lifestyle factors, including physical fitness, well-being…

2. What is the rationale for the genetic analysis? How do these assessments relate to the study aims and hypotheses?
We thank you for highlighting this omission and agree that the rationale could be improved in the manuscript.
We have inserted the following statement in the introduction:
Sleep is essential for human health however the mechanisms of sleep regulation are still not well established. There are limited data on objectively measured sleep and genetic variants that influence sleep traits such as chronotype [5].
Circadian rhythms have been shown not only to regulate sleep but several other physiological functions, including body temperature, physical activity, mood, and cognition. These processes are controlled by circadian clock genes. Conversely the timing of behaviours such as sleep, exercise, and food intake influence circadian rhythms, including clock gene expression [6-7]
We have inserted the following statement in the sub-study methods page 7
From the viewpoint of elucidating physiological mechanisms and managing disease risk, it is important to examine the relationship between chronotype and social jetlag and circadian rhythms, including clock gene expression. We will use the analysis of clock genes from a venous blood sample to examine the reciprocal impact of behaviour on circadian rhythm.
3. What is the rational for 8-days of accelerometer wearing as opposed to the recommended 10 or 14 days? Two weekend assessments are necessary to fully examine social jet lag metrics.
The rationale for 8-days accelerometer wear is to ensure that we do not over burden patients and to follow our department's standard operating procedures for this device. Further, this is in-line with the duration collected by Biobank who collect up-to 7 days of data. To our knowledge a significant portion of the literature based around social jet lag is based on subjective data and that report for objective measures averages around 7 days wear time. However, we do not disagree that two weekends would be more accurate and would be grateful for the reviewer to provide any published work on standards for the collection of data for objective measures of social jet lag and we will consider extending wear-time in a future protocol amendment.
4. Why is chronotype not being calculated from the accelerometer data? An objective assessment of chronotype would be superior?
This is a valuable point and we apologise for the oversight. It is in fact our intention to report both self-report and objectively measured parameters of sleep however, we agree this hasn't come across very clearly. Please note that we are measuring mid-sleep time from the accelerometer data which could be described as an 'objective' measure of chronotype, but we prefer to call it 'mid-sleep time' as has been done previously. This recognises that other factors impact on chronotype, more of which are captured in the validated MEQ.
We have amended the manuscript to reflect this.
Page 5, paragraph 2, line 4 we have added.
…definitions for this construct [16, 19, 20]. Mid-sleep time (as an objective measure of chronotype) and other sleep parameters will calculated from the accelerometer data.

5. The authors are strongly encouraged to consider household and environmental determinants of chronotype (and sleep in general) including (but not limited to) family composition, bedroom climate, neighbourhood factors, and geographic positioning. Omission of these variables limits the scientific rigor of this study.
This is a very valid point and we are seeking external advice (Prof A Hansel, Director of the Centre for Environmental Health and Sustainability, University of Leicester) on the most robust but pragmatic way to collect air quality, noise pollution, light pollution to permit us to use these as co-variates and to calculate exposure to light at night, a known risk factor for obesity [8]. We are collecting postal codes and thus geographical positioning and the above factors could be determined. We will in addition be

considering adding the following into the clinical record form: family composition, mobile phone/device usage before bed/in the bedroom i.e. blue light, presence of a bed partner, if bed partner disturbs sleep – how/how frequently and 'free text' – other items that may disturb your sleep on a regular basis. Finally we will, as per Park 2019 et al, consider including other measures of Artificial Light At Night (ALAN) again in the CRF.

These items are subject to future amendment to the protocol and external advice on methodology.

Whilst it is a valid point to include measure of bedtime climate due to limited funding we are not in a position to collect this data and do not feel asking participants about the temperature of their bedrooms would not be very reliable. Therefore, in any outcomes papers we will acknowledge this as a limitation.

6. It is not clear why these researcher questions were not just presented to the UK biobank?
The UK biobank was not chosen for these analyses because whilst there are analyses being conducted and published from UK biobank data in this area our local population provides an ethnic diversity that is not available from biobank. Further, sleep diaries have been collected therefore sleep estimates from accelerometer data we calculate are potentially more robust than biobank who have not collected these. In addition our data include self-compassion questionnaires and physical function tests. The data in this current study also serve as a test bed for future intervention studies in this patient population.

7. There are typos and formatting errors in the references.
We thank the reviewer for acknowledging this we have corrected accordingly.

References (for this response please note they have been included in the main text)
[1] Yates T, et al. Eur Heart J 2017 Nov 14;38(43):3232-3240
[2] Pavasini R, et al. BMC Med 2016 Dec 22;14(1):215-016-0763-7
[3] Fried LP, et al. J Gerontol A Biol Sci Med Sci 2001 Mar;56(3):M146-56
[4] Chao CT, et al. Cardiovasc Diabetol 2018 Sep 27;17(1):130-018-0772-2
[5] Jones SE, et al. Nature Coms 2019: 10.1585
[6] Garaulet M, Madrid JA. Adv Drug Deliv Revs 2010;62:967-978
[7] Takahashi M, et al. Scientific Reports. 2018 Jul 5;8(1):10152.[8] Park M, et al. doi:10.1001/jamainternmed.2019.0571
Reviewer 2
1. The criteria for person 's chronotype must be clear.
Thank you for this comment the methodology that we are using to determine chronotype has been validated. We are adding additional strength to these data by also collecting accelerometer data to calcite mid-sleep point (see above) as an objective measure of chronotype.

2. People's lifestyles change. Therefore, there are many limitations to the interpretation of the results.
Thank you for this important observation. In a cross-sectional study you are confounded and unable to infer causality. A prospective design would be of benefit however, limited funding and time-restraints do not permit this. However, this will be a rich dataset that will provide some insight in to sleep and other lifestyle behaviours and physiology.